

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 9/00, 9/14</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/03785</b> <b>(43) International Publication Date:</b> <b>9 February 1995 (09.02.95)</b>
<b>(21) International Application Number:</b> <b>PCT/US94/08551</b> <b>(22) International Filing Date:</b> <b>27 July 1994 (27.07.94)</b>  <b>(30) Priority Data:</b> <b>08/100,956      3 August 1993 (03.08.93)      US</b>  <b>(71) Applicant:</b> <b>WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).</b>  <b>(72) Inventors:</b> <b>LECH, Stanley; 46 Cherokee Avenue, Rockaway, NJ 07866 (US). DENICK, John, Jr.; 413 Springdale-Greendell Road, Newton, NJ 07860 (US). SCHOBEL, A., Mark; 307 Van Nest Road, Flemington, NJ 08822 (US).</b>  <b>(74) Agents:</b> <b>ALMER, Charles, W., III; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.</b>		<b>(81) Designated States:</b> <b>AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</b>  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> <b>PLEASANT TASTING EFFERVESCENT COLD/ALLERGY MEDICATIONS</b>		
<b>(57) Abstract</b>  A pleasant tasting, effervescent cold/allergy medication is provided in a solid tablet form. Bitter tasting decongestants, antihistamines, antitussive and expectorants are effectively taste masked using a magnesium trisilicate/fumed silica adsorbate which is undetectable during dissolution in the mouth yet provides a high degree of drug bioavailability when it reaches the acidic conditions of the stomach.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Pleasant Tasting Effervescent  
Cold/Allergy Medications

Field of the Invention

The present invention relates generally to cold and allergy medications that provide relief from the symptoms such as itchy, watery eyes, runny nose, clogged sinuses and the like in an orally administered form that is pleasant tasting and easily ingested.

Background of the Invention

Traditionally, cold and allergy medications are administered in tablets or capsules which for most people are easily swallowed with a glass of water or other beverage. Certain patients however, do not find tablet or capsule dosage forms particularly easy to swallow and therefore are not likely to comply with any therapeutic regimen requiring them. Such patients, in particular children, the aged and the mentally ill who gag, choke or simply refuse to swallow pills or capsules, need other alternative ways to deliver the medication without having to resort to intravenous or intra-muscular injections.

Obviously, many medications may be and are orally administrable in liquid elixir and syrup forms but again, these are not often desirable as the liquid carrier may present dissolution problems with respect to the active and/or the active itself may be bitter tasting so that any liquid delivery of the medication tastes terrible. This is often worsened by the lingering after taste as the liquid coats the mouth, throat and tongue. Moreover, the bulky bottles and packaging

necessary for liquid preparations are an inconvenience in certain circumstances.

There is a need for a dosage form of medication that may be packaged and administered as a solid tablet form, yet is still easily taken and swallowed by the patient.

Chewable tablets are one way in which this end has been achieved. United States Patent No. 2,887,437 relates to a chewable or swallowable tablet for vitamins that is flavored and generally acceptable to most children. Another approach to this end is the use of an effervescent tablet that self disintegrates when placed in the mouth as it comes in contact with the water component of saliva. The tablet "fizzes" as a gas such as carbon dioxide is released therefrom and this generally produces a very pleasing organoleptic sensation which, when combined with the simultaneous release of flavors, makes taking the medication "fun" for children and may enhance patient compliance.

Effervescent administration of active agents is not a new phenomena in the pharmaceutical arts and numerous compositions have been prepared utilizing this form of technology. United States Patent No. 4,962,417 to Howell and U.S. Patent No. 4,753,792 to Aberg disclose effervescent dental tablets that foam in the mouth and provide a tooth-cleansing action U.S. Patent No. 4,613,497 to Chavkin discloses an effervescent medicinal delivery system that is swallowed whole and foams in the stomach in order to provide release of the drug for absorption. U.S. Patent No. 4,687,662 to Schobel discloses a carbonate-acid based effervescent tablet for the administration of an

analgesic such as acetaminophen or ibuprofen through dissolution in water. However, none of these are designed to dissolve in the mouth so as to render the active immediately and easily swallowable.

EPO Patent Appln. No. 396,335 to Bolt discloses and claims a chewable medicinal tablet comprising a pharmaceutical active dispersed in a chewable base comprised of mannitol with an effervescent reaction system such as citric acid/sodium bicarbonate. The system serves to taste mask any bitter tasting drugs and a disintegrating agent such as microcrystalline cellulose may also be incorporated so as to allow for the dispersion of the active in water.

United States Patent No. 5,055,306 to Barry discloses an effervescent medicinal tablet with sustained release properties in which the tablet is comprised of an agglomeration of granules consisting of an active core coated with a water insoluble but water swellable acrylic polymer and a hydroxylated cellulosic derivative. It is asserted that as the tablet is chewed and/or dissolved in the mouth, any bad taste due to the pharmaceutical active is effectively masked by the polymer coating and effervescence until the drug reaches the stomach.

United States Patent No. 4,940,588 to Sparkes et. al. discloses a controlled release powder comprising a pharmaceutical active that is dispersed as micro-particles in at least one non-toxic polymer. An effervescent tablet is suggested as one possible carrier vehicle for the powder, but little else is pursued in this area.

United States Patent No. 5,178,878 to Wehling

et. al. teaches and discloses an effervescent tablet for the oral administration of a wide variety of drugs and other active pharmaceutical agents. The tablets are dissolved in the mouth and the active agent of choice is microencapsulated for dissolution and absorption in the stomach. The microcapsules allegedly provide a taste-masking function for bitter-tasting drugs. However, the tablet must not be chewed or crushed within the mouth since this would cause a rupture of the microcapsules and a release of the actives therein which would result in a bitter, unpleasant taste and a drawback to patient compliance. Moreover, microencapsulated drugs tend to have slow and unpredictable release profiles.

It is an object of the present invention to provide an orally administered effervescent medication for the relief of cold, sinus and allergy symptoms that is both pleasant tasting and rapidly disintegratable for enhanced drug bioavailability. It is a further object of the present invention to provide a solid dosage form of medication that provides a pleasant organoleptic mouthfeel through the effervescent disintegration thereof and also taste masks otherwise bitter tasting drugs which are readily available for absorption into the system.

#### Summary of the Invention

The present invention provides a pleasant tasting, organoleptically pleasing medication for the relief of colds, sinus and allergy by taste-masking a bitter-tasting pharmaceutical such as a decongestant, antihistamine and/or expectorant by

adsorption of the drug(s) onto a complex silica adsorbate and combining the resultant mixture with a carbonate-acid effervescent system.

#### Detailed Description of the Invention

Decongestants, antihistamines and expectorants are generally bitter tasting chemical compositions that must be encapsulated or taste-masked in some fashion when orally administered in order to allow them to pass through the mouth undetected for dissolution and absorption in the stomach. The problem with most attempts by the prior art to do this is that they also hamper the release of the drug and hence its bioavailability to the system which delays any relief provided thereby. The present invention comprises adsorbing any or all of the bitter tasting drugs onto a complex magnesium trisilicate and then mixing the drug carrier system thus formed with an effervescent component comprised of a carbonate-acid reaction system which is then dried and tableted for oral administration.

Complex magnesium trisilicate adsorbates are well known in the art and both their composition and method of preparation are clearly set forth and described in United States Patent No. 4,581,232 to Peters et. al. and U.S. Patent No. 4,711,774 to Denick et. al., both of which are hereby incorporated by reference. The trisilicate powder is comprised of many flake-like masses which hold the active drug within interstitial crevices. By containing the drug in this manner, the adsorbate acts to render bitter tasting drugs tasteless in liquid, tablet and chewable dosage forms which then become readily bioavailable when

the adsorbate reaches the lower acid pH of the stomach. The drug adsorbate by itself however, does not possess a particularly pleasant taste or mouthfeel that would appeal to children or adults for that matter.

It has been unexpectedly and surprisingly found that by combining the complex magnesium trisilicate with a fumed silica such as Cab-o-sil®, Cabot Co., Boston, Massachusetts the bitter, bad tasting drugs such as antihistamines and decongestants can be placed within a readily disintegratable vehicle such as an effervescent tablet. As the tablet effervesces in the mouth, the drug is released for swallowing in a form that is highly bioavailable for later absorption in the stomach but taste-masked so as to inhibit the perception of the bad tasting actives prior to the drug being swallowed. It is readily absorbed in the stomach as the lower pH environment breaks the complex down.

The drugs of interest are first adsorbed onto the flake-like structures of the magnesium trisilicate by methods known in the art (see Peters et. al. '232). Prior to drying however, fumed silica that is commercially available as Cab-o-Sil® EH5 is added and mixed until granules are formed. The adsorbate, comprised of the flaked magnesium trisilicate, the drug disposed therein and the fumed silica disposed thereon is dried to a LOD of not more than 2.0%. This adsorbate serves as the active component about which the effervescent tablet is made.

The drug adsorbate is then combined with an effervescent disintegration agent which dissolves rapidly and completely once the tablet is placed



within the patients mouth without the need for any chewing or voluntary muscular contraction such as sucking. The effervescence is generated by a combination of an alkali metal salt of bicarbonate or carbonate with an edible food grade carboxylic acid that produces a chemical reaction when the composition contacts the water component of saliva in the mouth. This reaction generally results in the release of carbon dioxide gas which produces the fizzy or bubbly sensation of effervescence. Suitable alkaline earth metal salts of bicarbonate include sodium bicarbonate, sodium carbonate, potassium carbonate and bicarbonate, calcium carbonate and bicarbonate and the like. Suitable food grade acids include citric acid, tartaric acid, malic acid, adipic acid, fumaric acid, succinic acid and mixtures thereof. Preferably, the effervescent composition of the present invention will be comprised of a mixture of sodium bicarbonate and citric acid.

The combination of the drug adsorbate and effervescent composition provides for an oral delivery system for otherwise bitter tasting medicaments that is both pleasant tasting and organoleptically pleasing due to the release of gas by the chemical reaction. Generally, the carbonate and acid are mixed and employed in amounts that will release about 20 ccs. to about 120 ccs. of gas per tablet. Additional sweeteners, flavors and the like may also be added in order to make the tablet even more pleasing to the taste and as additional aids in the taste masking of the bitter tasting drugs.

Whereas, the delivery system of the present invention may be used to taste mask and deliver

nearly any suitable orally administrable bitter tasting drug, the preferred pharmaceutical actives are decongestants, antihistamines and expectorants which by themselves are especially bitter tasting yet provide the needed relief to allergy, cold and flu symptoms. More preferably, the present invention will comprise a drug adsorbate in which a decongestant, pseudoephedrine hydrochloride and an antihistamine, diphenhydramine hydrochloride are adsorbed onto a magnesium trisilicate/fumed silica adsorbate which is then combined with the carbonate/carboxylic acid mixture to form the orally administrable effervescent tablet which provides a dual action form of relief. Optionally, an antitussives such as dextromethorphan or dextromethorphan hydrobromide and/or an expectorant such as guaifenesin may be added.

The decongestant and antihistamine may be added in amounts in a ratio from about 4:1 to about 1:4 respectively, and in amounts conventionally called for or required as per the dosage regimen involved. The usual dosage of the decongestant pseudoephedrine hydrochloride is generally about 15 mg. to about 60 mg. per tablet, or from about 1.0% to about 85% by weight while the antihistamine diphenhydramine hydrochloride is generally employed in amounts of from about 12.5 mg. to 25 mg. per tablet. Together, the actives generally comprise from about 1.0% to about 70% of the entire cold/sinus composition by weight. When an antitussive such as dextromethorphan hydrobromide or an expectorant such as guaifenesin are included, these are generally incorporated in amounts of from about 10 mg. to about 30 mg. per

tablet and from about 50 mg. to about 200 mg. per tablet, respectively.

The magnesium trisilicate composition is comprised as set forth in the Peters et. al. '232 patent and is combined with the fumed silica in approximately a 1:1 ratio of trisilicate/silica on a weight basis, respectively. The bicarbonate or carbonate salt and acid are also combined in approximately a 1:1 to approximately a 4:1 weight ratio to ensure a complete effervescent reaction during administration.

In general, the amount of carbonate salt/carboxylic acid composition used in the formation of the tablets of the present invention will comprise from about 5% to about 90% by weight of the entire tablet composition. Preferably, the effervescent reactants will comprise from about 15% to about 30% by weight of the total weight of the tablet and most preferably in an amount of from about 20% to about 25% by weight of the composition.

The amounts of effervescent composition employed should be enough to create a distinct fizzing or bubbling sensation within the mouth as the tablet disintegrates. To provide an adequate sensation in this manner, the amount of effervescent material should provide from about 10 ccs. to about 100 ccs. of carbon dioxide gas per tablet, and preferably, from about 20 ccs. to about 40 ccs. of gas per tablet.

The adsorbate/effervescent cold/sinus tablets of the present invention will preferably also include sweeteners, flavors, colorants, binders, fillers, lubricants, tableting agents and the like to aid in the taste masking and the tablet

formation process.

Suitable sweeteners include those sweeteners both natural and artificial well known in the art such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof. These may be utilized in amounts from about 5% to about 30% and preferably from about 5% to about 20% by weight of the tablet composition. Water soluble artificial sweeteners such as saccharin and saccharin salts such as sodium or calcium, cyclamate salts, acesulfame-K, aspartame and the like and mixtures thereof may be utilized in amounts from about 0.001% to about 5% by weight of the tablet composition.

Flavorants may also be added to enhance the overall taste perception and these include both natural and artificial flavors, mints such as spearmint, peppermint and menthol, vanilla, artificial vanilla, chocolate, artificial chocolate, cinnamon, various fruit flavors, both individual and mixtures thereof may be utilized in amounts of from about 0.5% to about 5.0% by weight of the total weight of the final tablet composition.

Colorants useful in the present invention include pigments which may be incorporated in amount up to about 6% by weight of the composition. A preferred pigment, titanium dioxide, may be incorporated in amounts up to about 1%. Also, the colorants may include other dyes suitable for food, drug and cosmetic

applications such as F.D.&C. dyes and the like. Such dyes are generally present in amounts up to about 0.25% and preferably from about 0.05% to about 0.2% by weight of the tablet.

Decolorizing agents such as sodium metabisulfite, ascorbic acid and the like may be incorporated into the tablet composition to prevent color changes due to aging. In general, amounts up to about 0.25% and preferably from about 0.05% to about 0.2% by weight of the tablet are used.

The following examples are provided to better demonstrate and more particularly define specific embodiments of the present invention. They are for illustrative purposes only, and it is recognized that there are many possible variations and changes that may be made of minor nature that nevertheless render arguably different compositions. It must be recognized that these variations and alternatives are also considered as falling within the spirit and scope of the present invention as recited by the claims that follow.

#### Example I

Twenty-five grams of diphenhydramine hydrochloride (12.5 mg/tab), 30 gms. pseudoephedrine hydrochloride (30 mg/tab), and 30 gms. dextromethorphan hydrobromide (15 mg/tab) and 240 gms. polyethylene glycol (120 mg/tab) a lubricant, were dissolved in 400 mls. distilled water. 230.0 grams of Cab-o-Sil EH5 (115 mg/tab) and 230.0 grams magnesium trisilicate adsorbate (115 mg/tab) were charged into a high shear mixer (Fitzpatrick-Kelly, S. Plainfield, N.J.) to which the active solution was added slowly. The

adsorbate was mixed until distinct granule formation occurred. The adsorbate was then dried in a hot air oven at about 60°C for about 5.0 hours until the composition reached an L.O.D. of less than 2.0%

The dried adsorbate granules were then milled using a comil equipped with .032 inch screen and a .25 inch spacer. The adsorbate granules thus formed were then mixed with the effervescent mixture comprising a binder, mannitol (311 mg./tab), sodium bicarbonate (80 mg./tab) citric acid (50 mg./tab) and tartaric acid (30 mg./tab) in a twin-shell blender (Fitzpatrick-Kelly, S. Plainfield, N.J.) and mixed until the granules were completely coated by the effervescent powder to insure proper homogeneity. To this was then added the sweeteners and flavors such as aspartame (7.5 mg./tab) acesulfame-K (8.0 mg./tab), and natural cherry extract (10.0 mg./tab). These were mixed continuously for an additional fifteen (15) minutes during which time magnesium stearate (6.0 mg./tab) a lubricant/tabletting agent is added. The mixture was then removed from the blender and the adsorbate-effervescent powder was compressed into 900 mg. tablets using a standard hand tablet press.

The tablets when taken orally displayed a high degree of effervescence ("fizziness") and upfront cherry flavor with no noticeable bitter aftertaste attributable to either the pseudoephedrine HCl, diphenhydramine HCl or dextromethrophan Hbr.

What We Claim Is:

1. A cold/allergy sinus medication comprising a decongestant/antihistaminic adsorbate in a pleasant tasting, mildly effervescent tablet.
2. The cold/allergy sinus medication of claim 1 wherein said adsorbate is comprised of a carrier material selected from the group consisting of magnesium trisilicate, fumed silica, and mixtures thereof.
3. The cold/allergy medication of claim 2 wherein said decongestant is selected from the group consisting of pseudoephedrine hydrochloride.
4. The cold/allergy medication of claim 3 wherein said antihistamine is selected from the group consisting of diphenhydramine hydrochloride.
5. The cold/allergy medication of claim 4 wherein said effervescence is generated by an effervescent composition comprising an alkali earth metal salt of carbonate and an edible food grade carboxylic acid.
6. The cold/allergy medication of claim 5 wherein said alkaline earth metal salt of carbonate is selected from the group consisting of sodium carbonate and bicarbonate, potassium carbonate and bicarbonate and mixtures thereof.
7. The cold/allergy medication of claim 6 wherein said carboxylic acid is selected from the group consisting of citric, tartaric, malic, adipic, fumaric, succinic, and mixtures thereof.

8. The cold/allergy medication of claim 7 wherein said effervescent agent is comprised of a mixture of sodium bicarbonate and citric acid.

9. The cold/allergy medication of claim 7 further comprising a pharmaceutically acceptable amount of excipients selected from the group consisting of sweeteners, flavors, colorants, lubricants, binders, acidifiers, sugar alcohols, tableting agents and mixtures thereof.

10. The cold/allergy medication of claim 9 further comprising an antitussive.

11. The cold/allergy medication of claim 10 wherein said antitussive is selected from the group consisting of dextromethorphan Hbr, and mixtures thereof.

12. The cold/allergy medication of claim 11 further comprising an expectorant.

13. The cold/allergy medication of claim 12 wherein said expectorant is selected from the group comprising guaifenesin.

14. The cold/allergy medication of claim 14 wherein said decongestant/antihistamine adsorbate comprises from about 1.0% to about 85% by weight of the entire cold/allergy medication.

15. The cold/allergy medication of claim 14 wherein said decongestant comprises from about 1.0% to about 85% by weight of total weight of the adsorbate composition.



16. The cold/allergy medication of claim 15 wherein said antitussive comprises from about 1.0% to about 85% by weight of the total weight of the adsorbate composition.

17. The cold/allergy medication of claim 16 wherein said expectorant comprises from about 1% to about 85% by weight of the entire composition.

18. The cold/allergy medication of claim 17 wherein said fumed silica comprises from about 5.0% to about 7.0% by weight of the total weight of said adsorbate composition.

19. The cold/allergy medication of claim 18 wherein the amount of gas released by said effervescent agent upon dissolution ranges from about 10 ccs./tablet to about 100 ccs./tablet.

20. A mildly effervescent, pleasant tasting cold/sinus medication comprising a decongestant/antihistamine adsorbate consisting essentially of diphenhydramine hydrochloride, pseudoephedrine hydrochloride, magnesium trisilicate and fumed silica.

21. The cold/sinus medication of claim 20 wherein said effervescence is created by an effervescent composition consisting of an alkaline earth metal salt of carbonate and an edible food grade carboxylic acid.

22. The cold/sinus medication of claim 21 wherein said effervescent composition is comprised of a mixture of sodium bicarbonate and citric

acid.

23. The cold/sinus medication of claim 22 wherein said decongestant and said antihistamine comprise from about 1.0% to about 70% by weight of the total weight of the adsorbate composition.

24. The cold/sinus medication of claim 23 wherein said adsorbate further comprises an antitussive selected from the group consisting of dextromethorphan hydrobromide and mixtures thereof.

25. The cold/sinus medication of claim 24 wherein said adsorbate further comprises an expectorant selected from the group consisting of guaifenesin.

26. The cold/sinus medication of claim 25 wherein said magnesium trisilicate comprises from about 1.0% to about 99.0% by weight of the total weight of the adsorbate composition.

27. The cold/sinus medication of claim 26 wherein said fumed silica comprises from about 99% to about 1.0% by weight of the total weight of the adsorbate composition.

28. The cold/sinus medication of claim 27 wherein said antihistamine and said decongestant are mixed in the adsorbate in a ratio by weight of from about 1:4 to about 4:1, respectively.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/08551

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K9/00 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 085 376 (BAYER AG) 10 August 1983 see claims 1,2 see page 3, line 3 - line 22 see page 8, line 11 - page 9, line 13 see page 10, line 9 - line 24 ---	1-3
Y	EP,A,0 239 542 (WARNER-LAMBERT COMPANY) 30 September 1987 cited in the application see example 4 see page 4, line 9 - line 26 see page 7, line 62 - line 65 --- -/--	1-28

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 November 1994

Date of mailing of the international search report

2. 12. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+ 31-70) 340-3016

Authorized officer

Ventura Amat, A

## INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 94/08551

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 132 472 (WARNER LAMBERT COMPANY) 13 February 1985 see claims 1,2 see page 2, line 1 - line 3 see page 3, line 25 - page 5, line 5 see page 7, line 20 - line 23 see examples 1,4,5 -----	1-28

## INTERNATIONAL SEARCH REPORT

Intern: 1 Application No  
PCT/US 94/08551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0085376	10-08-83	DE-A- 3203443	11-08-83
		AU-A- 1087883	11-08-83
		JP-A- 58133827	09-08-83
-----			
EP-A-0239542	30-09-87	US-A- 4711774	08-12-87
		AU-B- 574605	07-07-88
		AU-A- 7069187	01-10-87
		CA-A- 1282328	02-04-91
		JP-B- 6076316	28-09-94
		JP-A- 62238215	19-10-87
		US-A- 4758424	19-07-88
		US-A- 4758425	19-07-88
		US-A- 4761274	02-08-88
ZA-A- 8701660	27-08-87		
-----			
EP-A-0132472	13-02-85	US-A- 4581232	08-04-86
		AU-B- 563740	23-07-87
		AU-A- 2068983	24-01-85
		CA-A- 1207232	08-07-86
		JP-C- 1776857	28-07-93
		JP-B- 4065811	21-10-92
		JP-A- 60112722	19-06-85
		US-A- 4632822	30-12-86
		US-A- 4632823	30-12-86
		US-A- 4632821	30-12-86
		US-A- 4643898	17-02-87
		US-A- 4642231	10-02-87
		US-A- 4647459	03-03-87
		US-A- 4643892	17-02-87
		US-A- 4647450	03-03-87
		US-A- 4650663	17-03-87
		US-A- 4647449	03-03-87
US-A- 4649041	10-03-87		
-----			